

Pharmacokinetics of intranasal scopolamine gel formulation during antiorthostatic bed rest, a microgravity analog

Rajendra P. Singh¹, Vernie R. Daniels², Camille J. Crady², H. Derendorf¹ and L. Putcha³

¹Department of Pharmaceutics, University of Florida, Gainesville, FL; ²Wyle Integrated Science & Engineering, Houston, TX; ³NASA Johnson Space Center, Houston, TX



ABSTRACT

Statement of Purpose, Innovation or Hypothesis: Space Motion sickness (SMS) is a long-standing problem for astronauts on both short and long duration space flights. Scopolamine (SCOP) is frequently used for the treatment of motion sickness (MS), and is available as transdermal patch and tablet dosage forms. These formulations of SCOP are ineffective for the treatment of SMS. Intranasal dosage forms are noninvasive with rapid absorption and enhanced bioavailability, thus allowing precise and reduced dosing in addition to offering rescue and treatment options. An intranasal gel dosage formulation of scopolamine (INSCOP) was developed and pharmacokinetics (PK) and bioavailability were determined in clinical trials with human subjects under IND guidelines.

Description of Methods and Materials : The present clinical trial compares PK and bioavailability of INSCOP in 12 normal, healthy subjects (6 male/ 6 female) during ambulation (AMB) and antiorthostatic bed rest (ABR) used as a ground-based microgravity analog. Subjects received 0.2 mg and 0.4 mg doses of INSCOP during AMB and ABR in a 4-way crossover design.

Data and Results : Results indicated no difference between AMB and ABR in PK parameters after 0.2 mg dose, Clearance (Cl) decreased with a concomitant increase in maximum concentration and area under concentration-versus-time curve (AUC) during ABR after the 0.4 mg dose.

Interpretation, Conclusion or Significance : The difference in AUC and Cls at the higher (0.4 mg) but not the lower dose (0.2 mg) during ABR suggests that ABR may affect metabolism and/or clearance of INSCOP at higher doses . These results indicate that dosing adjustment may be required for treatment of SMS with INSCOP in space.

INTRODUCTION

Motion sickness (MS) is a long-standing problem for space travelers on short and long duration space flight. Oral antiemetics are not very effective in space due to poor bioavailability.

Scopolamine (SCOP) is the most frequently used drug by recreational travelers, with patches and tablets currently available on the market. Common side effects of antiemetics, in general, include drowsiness, sedation, dry mouth and reduced psychomotor performance. Severity and persistence of side effects are often dose related. Side effects can be detrimental in high-performance demanding settings, such as space flight, military.

Oral, injectable and transdermal formulations of SCOP are either invasive, unsuitable or ineffective for the treatment of space motion sickness. The intranasal dosage form of scopolamine offers great promise for the treatment of MS on Earth and in space:

- ❖ It is noninvasive
- ❖ Rapid absorption facilitates rescue and treatment options with the same formulation
- ❖ Enhanced and reliable bioavailability allows precise and reduced dosing options

METHODS

Study design

The study was randomized and crossover, with subjects (n=12) receiving the intranasal formulation under antiorthostatic bed rest conditions or ambulatory conditions, at doses 0.2 and 0.4mg. Plasma samples were collected at time points, once pre-dose and at 0.17, 0.33, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 hours post -dose.

Data Analysis

Pharmacokinetic parameters were calculated from the plasma concentration-time data by non-compartmental methods using WinNonLin standard edition, version 5.2. The peak plasma concentration (C_{max}) and time to peak concentration (T_{max}) were determined directly from the plasma profiles. The elimination rate constant (K_{el}) was calculated from the slope of the terminal phase of the plasma concentration-time plot. The area under the curve ($AUC_{0-\infty}$) was estimated by the linear trapezoidal method with extrapolation to infinity based on the concentration of the last time point measured divided by the terminal rate constant.

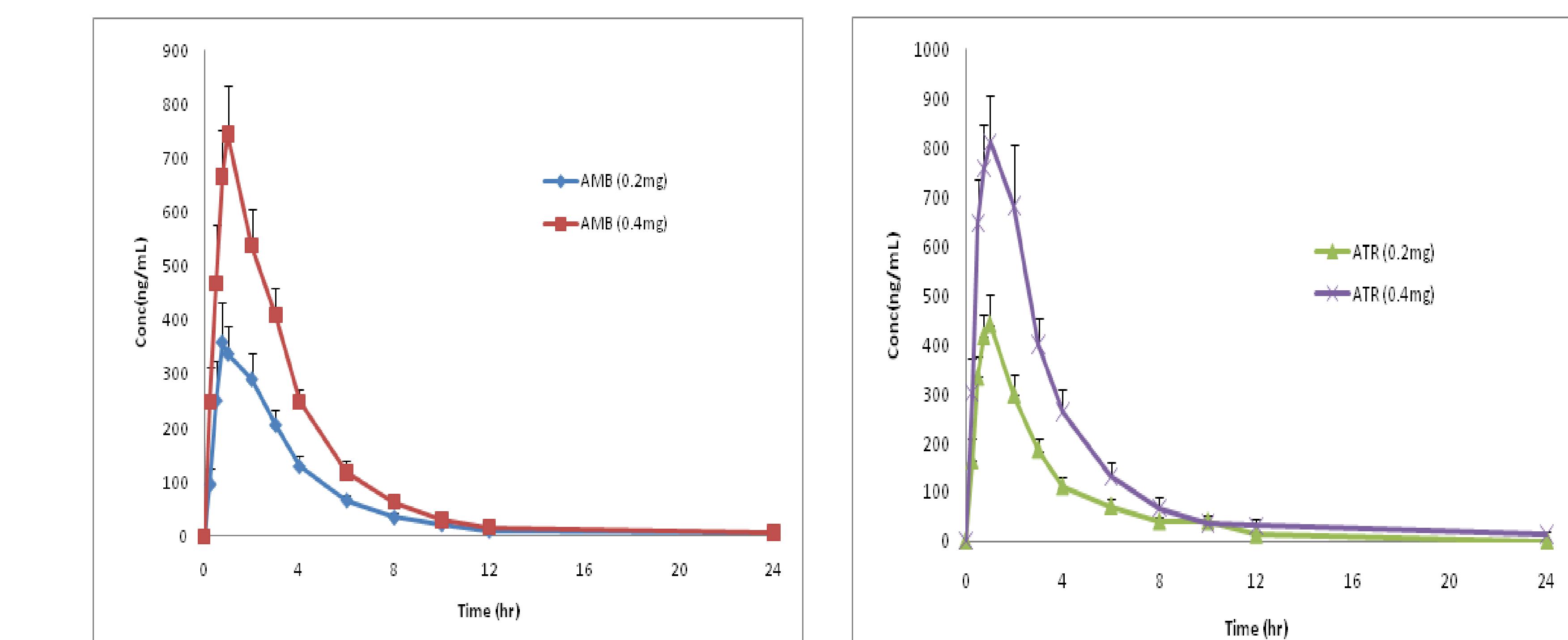
Bioequivalence of the two doses between control and ABR was determined at 90% CI using mean C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ with limits between 80.00% and 125.00%.

RESULTS

The plasma concentration time profiles were analyzed using the non-compartmental method. After administration of the 0.2mg dose of INSCOP during AMB and ABR, AUC values were similar with no significant difference at 95% CI. However, AUC values were significantly different after 0.4mg dose. All relevant PK parameter estimates are listed in **Table 1**.

The parameters were evaluated for bioequivalence between AMB and ABR. Results of this evaluation (table 2) showed that the two doses are not bioequivalent with ratios at 90% CI, and are outside the specified limits of 80 and 125%.

Figure 1. Mean plasma concentration time profiles of scopolamine after 0.2 and 0.4mg intranasal dosing during ambulatory and antiorthostatic bed rest conditions



RESULTS

Table 1. Pharmacokinetic parameters of INSCOP after administration to human subjects

| Dose | Parameters | Ambulatory | | Antiorthostatic Bed Rest | |
|--------|---------------------------|------------|---------|--------------------------|---------|
| | | Mean | SD | Mean | SD |
| 0.2 mg | $T_{1/2}$ (hr) | 3.23 | 1.95 | 2.80 | 1.15 |
| | T_{max} (hr) | 1.27 | 0.78 | 0.83 | 0.20 |
| | C_{max} (hr) | 409.53 | 234.43 | 464.83 | 208.10 |
| | AUC_{last} (hr.pg/mL) | 1364.85 | 969.56 | 1435.46 | 786.72 |
| | Cl/F (L/hr) | 163.78 | 74.4 | 152.87 | 69.97 |
| | Vz/F(L) | 706.02 | 504.34 | 531.56 | 167.77 |
| | AUC_{∞} (hr.pg/mL) | 1562.28 | 1077.64 | 1621.17 | 893.65 |
| 0.4 mg | $T_{1/2}$ (hr) | 3.14 | 4.36 | 5.02 | 4.89 |
| | T_{max} (hr) | 1.04 | 0.64 | 0.96 | 0.38 |
| | C_{max} (hr) | 810.66 | 329.20 | 897.88 | 398.44 |
| | AUC_{last} (hr.pg/mL) | 2642.24 | 1490.97 | 3106.12 | 2101.43 |
| | Cl/F (L/hr) | 167.79 | 59.11 | 144.83 | 61.17 |
| | Vz/F(L) | 526.63 | 198.51 | 826.47 | 724.75 |
| | AUC_{∞} (hr.pg/mL) | 2929.00** | 2012.18 | 3534.07** | 2462.53 |

Table 2 Bioequivalence of INSCOP between AMB and ABR conditions (CI Limits 80-125% ** P<0.05

| Dose | Parameters | Ratio | Lower CI | Upper CI | Power |
|--------|------------------|--------|----------|----------|--------|
| 0.2 mg | C_{max} | 121.98 | 86.05 | 172.93 | 0.2760 |
| | AUC_{0-t} | 111.87 | 76.31 | 164.01 | 0.2471 |
| | $AUC_{0-\infty}$ | 106.63 | 75.19 | 151.20 | 0.2757 |
| 0.4 mg | C_{max} | 110.14 | 84.09 | 144.27 | 0.3869 |
| | AUC_{0-t} | 112.72 | 80.89 | 157.09 | 0.2941 |
| | $AUC_{0-\infty}$ | 118.52 | 84.05 | 167.11 | 0.2815 |

CONCLUSIONS

After intranasal administration of scopolamine to human subjects during AMB and ABR conditions PK parameters were similar at the low dose (0.2 mg), but not at the high dose (0.4 mg) between the two conditions. Comparison of C_{max} and AUC values suggest that treatments between the two conditions were not bioequivalent when the 90% confidence intervals fell outside the specified limits of 80 and 125% for both doses tested.

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